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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,064	01/29/2004	Tony Peled	24024-506	5661

30623 7590 11/06/2008

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ATTN: PATENT INTAKE CUSTOMER NO. 30623
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,064	PELED ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *201,209,212-214,239,244 and 245* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *201,209,212-214,239,244 and 245* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/3/08, 5/13/08,4/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment to the claims filed on July 3, 2008, has been received and entered. Claims 1-200, 202-208, 210-211, 215-238, 240-243 have been canceled, while claim 201 has been amended. Applicants have also added claim 245 that is generally directed to elected invention

Claims 201, 209, 212-214, 239, 244 and 245 are pending in the instant application.

Election/Restrictions

Applicants' election of claims 201, 209-215, 217-231, 235, 238 and 239 (Group I) in the reply filed on October 25 was acknowledged. Applicants have also elected culturing the cells in presence of one copper chelator (claims 201), neonatal umbilical cord cells (claim 209), FLT-3 ligand (claim 212) and granulocyte colony-stimulating factor (claim 214) as election of species for the elected invention. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Election was made **without** traverse in the reply filed on October 25, 2006.

Claims 201, 209, 212-214, 239, 244 and 245 are under current examination.

Withdrawn-Claim Objections

The objection to claim 238 is withdrawn in view of cancellation of the claim.

Maintained -Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 201, 209, 212-214, 239, 244 remain rejected under 35 U.S.C. 112, first paragraph, and newly added claim 245 is also rejected under 35 U.S.C. 112, first paragraph , because the specification, while being enabling for a method of expanding an *ex vivo* population of $CD34^+$ hematopoietic stem cells in culture medium, while at the same time inhibiting differentiation of the said cell ex vivo in culture medium; said method comprising:(a) providing a hematopoietic mononuclear cells that are not enriched prior to culturing , (b) culturing the MNC *ex vivo* for a period greater than 7days in culture under conditions allowing the proliferation in presence of FLT3, IL-6, TPO and SCF, and at the same time inhibiting differentiation in presence of an effective amount of at least one copper chelator TEPA, which reduces intracellular available copper concentration in said cells; thereby expanding a population of said hematopoietic stem cells while at the same time inhibiting differentiation of said hematopoietic stem cells *ex-vivo* for a period greater than 7 days,

does not reasonably provide enablement for culturing mononuclear cells under conditions comprising any copper chelator at any concentration, in an undefined medium lacking cytokines as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed July 3, 2008 have been fully considered, but are not persuasive.

Applicants argue that the instant inventors have demonstrated that the inhibition of differentiation of hematopoietic stem and early progenitor cells by

copper chelators is the result of reduction of intracellular available copper concentration, and is not restricted to a specific chelator. Applicants also cite the teaching of Peled et al. (Expt. Hematol., 2004, 32, 547-555) showing that other linear polyamine chelators have same effect as TEPA on cultured hematopoietic stem cell.

In response, it is noted that rejection is based on several issues related to the absence of an enabling disclosure for *ex-vivo* culture and expansion and inhibition of differentiation of hematopoietic stem cells, for a period greater than 7 days under undefined culture conditions in the presence of any copper chelator any concentration. The guidance provided in the specification is limited to addition of TEPA (5-10 μM) chelator to non-purified MNC cultures in presence of 50ng/ml o f each of FLt3, IL-6, TPO and SCF. The culture analyzed over a period of greater than 7 days shows progressively increased the number of CD34+ cells, CD34+ colony-forming cells and CD34+CD38- cells (see example 1, pages 92-93; also see figure 1a, 1b and 2). The specification is silent however on the culture, expansion and prevention of differentiation of hematopoietic stem/progenitor cells in the presence of any copper chelator or at any concentration of any copper chelator other than TEPA 5-10μM, or in the absence of specific cytokine combinations for a period greater than 7 days. Examiner has cited references to show that the art of growing undifferentiated stem cell in culture is unpredictable because that the mechanisms that control the proliferation, expansion, and differentiation of stem cells are not yet completely understood particularly since even for the same stem cell type, various culture conditions do not render the same results. It is generally known that hundreds of cytokines have been identified, and most induce pleiotropic effects when administered to isolated cells *in vitro.* Such pleiotropism is increased when multiple different cytokines are simultaneously used, such as in the instant claims. Examiner has previously indicated that "[v]arious combinations of cytokines have profoundly different effects on... stimulation of self-renewal division of

hematopoietic stem cells in an, *ex vivo* culture (see Murray *et al.* (1999)Exp. *Hematol.* 27:1019-1028). Murray reference shows various combinations of cytokines have profoundly different effects at a specific concentration of each cytokine (see page 1020, col. 1, last line to col. 2, line 1). This was further evidenced by Peters et al. (Br. J. Haematol, 119:792-802; 2002) who tested a large series of culture conditions, including those used successfully with CB CD34+ cells, but only one of them sustained long-term, massive expansion of FL hematopoietic cells, reaching over $3xl0^7$-fold input cell number after - 150 days in culture. It is apparent that contrary to applicant's argument one of skilled in the art would have to make new discovery to determine right combination of early and late cytokine with appropriate concentration of copper chelator for expanding an ex vivo population of CD34+, Cd34+/CD38- HSC, while at the same time inhibiting the differentiation for a period of greater than 7 days.

With respect to applicants' argument that Peled (Expt. Hemtol, 2004, 547-555) in post filing art teaches that other linear polyamine chelators capable of reducing intracellular copper have the same effect as TEPA on cultured hematopoietic stem cells, it is noted that contrary to applicants' assertion claims are not limited to polyamine chelator. It is noted that claims read on any copper chelator that reduces intracellular copper concentration. In fact, Peled et al (Experimental Hematology, 2004, Vol.32, pages 547-555) specifically provide guidance only with respect to low-molecular-weight linear polyamine Cu chelator TEPA at a concentration that moderately reduced cell Cu content (by 20-30%) (Emphasis added) enabling ex vivo expansion of CD34+ cell in presence of cytokine SCf, FLT-l, TPO and IL-6. It was emphasized that neither specification nor prior art establishes any nexus between expansion of CD34+ cells in MNC to presence of any copper chelator other then that is exemplified in the instant application that reduces intracellular available copper to a level such that it facilitates expansion as well as inhibits differentiation at the same time of the CD34+ cells in a mixed

population of mononuclear cells. Moreover, at the time the invention was made it was generally known to one of skilled artisan that polyaminic chelate can be toxic (Burgada et al., Eur.J Org. Chem, 2001, pages 349-352, or Chelation Therapy, 2006, pages 1-5). In the instant case specification fails to provide representative number of structurally related compounds Cu chelator that are not toxic and thus can be used in the claimed method of ex vivo expanding a population of CD34+ cells from hematopoietic mononuclear cells that are not enriched prior to culturing. It is emphasized that Table 3 of US patent no 6,962,698 teaches transition metal chelator assay for determining the effect on MEL and HL-60 cell line, which could not be extrapolated to instantly claimed method of expanding CD34+ by culturing MNC in presence of cytokine and Cu chelator for a period of greater than 7 days. This is particularly important since examiner has previously cited art that showed cells incubated with TEPA and retinoic acid produced the same amount of superoxide anion as did the cells with retinoic acid, indicating that the cells still underwent differentiation, suggesting more work may be required to understand the role of copper chelator in expansion of HSC (page Percival et al Am J Clin Nutr. 1998, art of record 1066S, col. 2, para. 2). It is emphasized that an assay for finding a chelator is not equivalent to a positive recitation of *how to make* a chelator work in method of expanding a specific population of cell directly from MNC that is not enriched prior to culturing. Furthermore, specification acknowledges that while reducing the present invention to practice, it surprisingly and unexpectedly found that molecules such as copper chelator repress differentiation and stimulate and prolong proliferation of hematopoietic stem cells (see page 28, para. 4). The lack of guidance in the specification would force the skilled practitioner to guess as to how to practice the invention in a manner commensurate in scope with the claims. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not to find out how to use

it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. The specific elements contemplated by the specification in the method of expansion of hematopoietic stem cells from MNC that are not enriched prior to culturing in presence of specific combination of cytokine and TEPA were not discovered by Applicant, rather they are derived from the prior art based on reports of their function in expansion of CD34+ cells . Absent of evidence to the contrary, it is not clear that other elements would be functional in the same manner as they have been demonstrated in the instant application. It is noted that specific recitation of conditions that proliferations CD3+ cells and reduces intracellular copper concentration resulting in inhibiting the differentiation of CD34+ for a period greater than 7 days in the method of independent claims would obviate the basis of rejection.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 201, 209, 212-214, 238-239 and 244 rejected under 35 U.S.C. 112, second paragraph is withdrawn in view of amendments to the claims. Applicants arguments with respect to claim 201 for reciting insufficient antecedent basis for the term said hematopoietic stem cells is persuasive and therefore rejection is withdrawn.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 201, 209, 212-214, 239 and 244 remain rejected under 35 U.S.C. 103(a) and newly added claim 245 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Fietz et al (Bone Marrow Transplant. 1999 Jun;23(11):1109-15) or Wang et al (Sheng Wu Gong Cheng Xue Bao. 2002 May;18(3):343-7)and Peled et al (WO99/40783, 8/19/1999, IDS).

Applicants' arguments filed July 3, 008 have been fully considered but are not persuasive. Applicants argue that none of the references teach culturing mononuclear cells *ex-vivo* for a period greater than 7 days under conditions allowing for cell proliferation, thereby expanding a population of said cells for a period greater than 7 days. Applicants also submit that the skilled artisan would not combine the teachings of Feitz and Peled to reach the present invention with a reasonable expectation of success. Applicants cite McNeice et al., (Cytotherapy 2004;6:311-17) that describes the failure of expansion of hematopoietic stem cells from unselected cord blood mononuclear cells (See page 7 of the argument). Applicants also assert that Feitz failed to observe any significant increase in total or CD34+ cells with greater than 7 days culture of the unselected mononuclear cells, as required by the instant claims.

In response, it is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). Fietz et al teach a method to expand CD34+ hematopoietic cells by providing mononuclear cells that are not enriched prior to culturing the cells in presence of early and late acting cytokine to expand population of hematopoietic stem cells. It is noted that while the reference of Fietz et al shows overall increase in CD34+ cells is significant for the mononuclear cell fraction after one week of culture (see table 1), it is the reference of Peled that provide guidance of expanding cells beyond 7 days in presence of Cooper Chelator TEPA. It appears that applicants are arguing against the references individually, one cannot show nonobviousness by attacking

references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' assertion and citation of references (McNeice et al and Briddell et al) showing failure of expansion of hematopoietic stem cells from unselected cord blood mononuclear cells is not persuasive as these references are not commensurate with the scope of the claimed invention. It is noted that none of the references disclose expansion of cells in presence of copper chelator.

In the instant case, contrary to applicants' assertion, Peled et al. provide motivation as well as adequate guidance to one of ordinary skill in the art to include Copper chelator with low doses of early acting cytokine for expanding total number of cell, number of Cd34+ cells and clonability (as evidenced by Peled see figure 1-3 and table 1). Additionally, Peled et al also provided guidance with respect to long term effect of TEPA on proliferation and clonability by culturing cells in presence of TEPA for 3 weeks showing higher clonability (See page 23 and 24, also see claims 1, 14-16). The results disclosed by Peled suggest that TEPA inhibits erythroid differentiation.

Thus, in view of foregoing it is apparent that one of ordinary skill in the art would conclude that method of expanding a population of cells, while at the same time inhibiting differentiation of the cells, the method comprising the step of providing the cells with conditions for cell proliferation and, at the same time, for reducing a capacity of said cells in utilizing transition metals was known (see Peled et al , claims 1, 14).

Accordingly, in view of the teachings of Fietz and Peled, it would have been obvious for one of ordinary skill in the art that method of expanding CD34+ cells was recognized as part of ordinary capability of one of skill in the art. One of skill in the art would have been capable of applying this known technique of expanding CD34+ cell, total number of cell and clonability to the known method of culturing

unselected cells as in Fietz. The results would have been predictable to one of ordinary skill in the art as Peled has already disclosed that Copper chelator TEPA in presence of low doses of early acting cytokine results in expansion in total number of cell, Cd34+ cells and clonability in short as well as long term culture. Therefore, given that copper chelator such as TEPA was available for use to expand long term culture by inhibiting/delaying the differentiation of CD34+ cells through chelation of transition metal as per teaching of Peled, it would have been obvious for one of ordinary skill in the art to use copper chelator TEPA in the culture medium disclosed by Fietz with reasonable expectation of achieving predictable results of expanding CD34+ cell in culture of MNC. One who would practiced the invention would have had reasonable expectation of success because Fietz had already described a method of *ex vivo* expansion of blood mononuclear cells (MNCs), in presence of early and late acting cytokine for one to four week, while Peled described use of copper chelator such as TEPA that could facilitate expansion of CD34+ cells beyond one week by inhibiting differentiation of CD34+ cells. Thus, it would have only required routine experimentation to modify the method disclosed by Fietz to include TEPA in the culture medium as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Maintained-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In*

re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 201, 209, 212-214, 2239 and 244-245 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,169,605 for the reasons of record

Claims 201, 209, 212-214, 239 and 244-245 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 8-17, 19-22, 131, 123-131 of copending U.S. Patent Application No.: 10,418,639 for the reasons of record.

Claims 201, 209, 212-214, 239 and 244-245 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2-11,
and 23 of copending U.S. patent Application No.: 10/564777 for the reasons of record .

Applicants have indicated that they would consider filing terminal disclaimer upon notice of allowable subject matter in this application.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
AU 1632
/Valarie Bertoglio/
Primary Examiner, Art Unit 1632